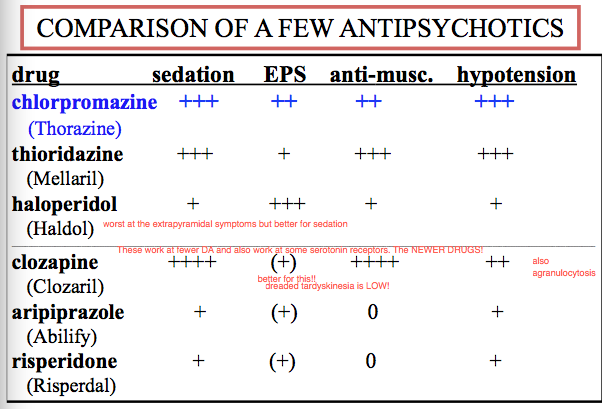
* **RESPIRATORY**
  + **Β-AGONISTS**
    - **EPINEPHRINE**
    - **TERBUTALINE**
    - **ALBUTEROL**
    - **SALMETEROL**
  + **ANTICHOLINERGICS**
    - **IPRATROPIUM BROMIDE**
  + **GLUCOCORTICOIDS**
    - **PREDNISONE**
    - **PREDNISOLONE**
    - **METHYLPREDNISOLONE**
    - **TRIAMCINOLONE**
    - **TRIAMCINOLONE ACETONIDE**
    - **BECLOMETHASONE**
    - **FLUTICASONE**
  + **LEUKOTRIENE RECEPTOR ANTAGONISTS**
    - **ZAFIRLUKAST**
    - **MONTELUKAST**
  + **5-LO INHIBITORS**
    - **ZILEUTON**
  + **METHYLXANTHINES**
    - **THEOPHYLLINE**
  + **MAST CELL STABILIZERS**
    - **CROMOLYN SODIUM**
  + **PROSTAGLANDINS**
    - **EPOPROSTENOL**
  + **ENDOTHELIN ANTAGONISTS**
    - **BOSENTAN**
  + **OPIOID AGONISTS**
    - **CODEINE**
    - **DEXTROMETHORPHAN**
  + **EXPECTORANTS**
    - **GUAIFENESIN**
* **NON-SELECTIVE CNS DEPRESSANTS**
  + **BARBITURATES**
    - **THIOPENTAL**
    - **PENTOBARBITAL**
    - **SECOBARBITAL**
    - **BARBITAL**
    - **PHENOBARBITAL**
  + **OTHERS**
    - **PROPOFOL**
    - **ETOMIDATE**
    - **KETAMINE**
    - **NON-BARBITURATE SEDATIVE HYPNOTICS—CHLORAL HYDRATE**
* **LOCAL ANESTHETICS**
  + **ESTERS**
    - **COCAINE**
    - **PROCAINE**
    - **BENZOCAINE**
    - **TETRACAINE**
  + **AMIDES**
    - **LIDOCAINE**
    - **BUPIVACAINE**
    - **LEVOBUPIVACAINE**
    - **ROPIVACAINE**
* **GENERAL ANESTHETICS**
  + **INHALATIONAL**
    - **HALOTHANE**
    - **ISOFLURANE**
    - **SEVOFLURANE**
    - **DESFLURANE**
    - **N2O**
  + **INTRAVENOUS**
    - **BARBITURATES**
    - **PROPOFOL**
    - **ETOMIDATE**
    - **NOT NON-SELECTIVE CNS DEPRESSANTS**
      * **OPIOIDS**
      * **BENZODIAZEPINE**
      * **KETAMINE**
* **ALCOHOLS**
  + **ETHANOL** 
    - Nonselective CNS depressant
    - Affects on GABAA (plus includes a type of this receptor in the cerebellum—ataxia), Inhibits Glu transmission, Action at NMDA receptor
    - Adverse: myocardial depression, vasodilation in CNS, peripheral vasodilation may be due to ↑ acetaldehyde
    - Fatty food delay abs
    - F>M
    - Metabolized by Alcohol DH
      * Mechanism is limited by NAD+
    - Zero order kinetics
  + **DISULFIRAM**
    - Inhibits Acetaldehyde DH🡪 accumulation of Acetaldehyde (flushing, HA, N/V, hypotension, etc)
    - Polymorphisms in this enzyme—Asians have ↓ so ↑ effects of alcohol--↑ acetaldehyde so when they drink a lot its like they are on disulfiram so they normally don't abuse alcohol
  + **METHANOL**—wood alcohol
    - Metabolized by alcohol DH🡪 formaldehyde and formic acid🡪 toxic to retina (blindness)
    - Tx: ethanol or fomeprizol
  + **ETHYLENE GLYCOL—**antifreeze
    - Metabolized by alcohol DH into axalic acid
    - Tx: ethanol or fomeprizol
  + **FOMEPIZOL—FO-ME-Pizol (FOr M-methanol and E-ethylene glycol intox)** 
    - Inhibits alcohol DH (polymorphisms in this too--↑ activity🡪 ↓ abuse)
  + **NALTREXONE**
    - Long acting Opioid antagonist—DON'T GIVE IF PT IS TAKING OPIOIDS
  + **ACAMPROSATE**
* **BENZODIAZEPINES**
  + *Functional tolerance (not metabolic) to some of the effects but NOT ALL*
  + **TRUE BENZODIAZEPINES**
    - **DIAZEPAM (VALIUM)**
      * Uses: Anxiolytic, Hypnotic, Anticonvulsant, Muscle Relax, Pre-anesthetic
      * MOA: Works at CERTAIN GABA­A receptors, binding to the benzo receptor ( γ2 subunit) ↑ their activity🡪 ↑ Cl coming in and ↑ inhibitory potential at post-syn site. GABA must be present.
      * Well abs (not IM), distributes well
        + IV—very rapid onset and short DOA due to distribution
      * COMPLICATED Biotransformation (dealk, hydroxyl🡪 3 active metabolite)
        + No induction of enzymes
        + Desmethyldiazepam is longest acting metabolite and it accumulates
        + Want to give this during WITHDRAW b/c want to give brain time to get used to drug free state
    - **FLUMAZENIL**
      * Competitive ANTAG at the BZ binding site on GABA­A receptor
      * NO action of its own
      * Uses: reversal of conscious sedation, tx of BZ OD.
    - **ANXIOLYTICS** (*all BZ’s are anxiolytic)*
      * **DIAZEPAM—**complicated biotransformation
      * **LORAZEPAM**
        + SIMPLE biotransformation!—CONJUGATION🡪 INACTIVE metabolite
      * **ALPRAZOLAM** (“antidepressant”)
        + SIMPLE biotransformation!—HYDROXYLATION then CONJUG. 🡪 Active🡪 rapidly inactive metabolite
    - **HYPNOTICS *(****↓ onset ↓ awakenings*)
      * *No tolerance develops*
      * **TRIAZOLAM—**short acting
        + SIMPLE biotransformation!—HYDROXYLATION then CONJUG. 🡪 Active🡪 rapidly inactive metabolite
      * **ZOLPIDEM—**selective for GABA­A receptor w/ an α1 subunit🡨MORE selective
      * ***\*\*better than barbiturates for sleeping!***
    - **ANTICONVULSANT (***can dev. tolerance*)
      * **DIAZEPAM—**medical emergency
        + Works fast
      * **LORAZEPAM**—medical emergency
        + longer action than diazepam
      * **CLONAZEPAM—**chronic tx
        + COMPLICATED BIOTRANSFORM.
    - **MUSCLE RELAXANT**
      * **DIAZEPAM—**↓ skeletal mm. tone
    - **PREANESTHETIC** *tolerance develops* 
      * **DIAZEPAM—**rapid recovery after single IV dose due to DISTRIBUTION
      * **MIDAZOLAM**—induction, not true anesthetic state
        + SIMPLE biotransformation!—HYDROXYLATION then CONJUG. 🡪 Active🡪 rapidly inactive metabolite
        + rapid recovery after single IV dose due to BIOTRANSFORMATION
  + **NON-BENZODIAZEPINE HYPNOTICS**
    - **ZOLPIDEM (AMBIEN)**
    - **RAMELTON (**RAMEY HAS A CRAZY SLEEP SCHEDULE (DSPS) SO HE TAKES MELATONIN, HE ACTS LIKE HES 12 girl (↓ TESTESTERONE ↑ prolactin)
      * Melatonin Agonist—promotes sleep
      * Indicated for Delayed sleep phase syndrome (DSPS)—circadian rhythm disorder
      * Metabolised by CYP1A2
      * Drug interactions: inhibited by fluvoxamine, INDUCED by rifampin
      * Adverse: ↓ testosterone, ↑ prolactin
  + **NON-BENZODIAZEPINE ANXIOLYTICS**
    - **BUSPIRONE—**I HAVE ANXIETY ABOUT TAKING THE BUS AND NOT MY BENZ!!
      * Partial agonist at 5-HT1A receptors
      * 1-3 weeks until onset of effects
      * drug interactions—HTN w/ MAOI—KIDS IN GRADES 3 & 4 CANT TAKE THE BUS SO MA (MAO) HAS TO TAKE THEM
        + interactions also w/ drugs that induce or inhibits CYP3A4 (it is metabolized by this)
* **PARKINSON’S DRUGS**
  + *↓ DA neurons in the substantia nigra pars compacta (↓ in nigrostriatal pathway) 🡪 ↓ inhibitory signaling from striatum to the SNpr/GPi🡪 ↑ activity of the SNpr/GPi (which is inhibitory) so ↑ inhibition to the thalamus🡪↓ cortical sitimulation 🡪 ↓ movements*
  + *Toxin induced Parkinsonism—MPTP!!*
  + **SUPPLY SUBSTRATE** 
    - **DOPAMINE**
      * Does not cross BBB
    - **LEVADOPA**
      * Transported into neurons and decarbox into DA by L-AAAD (DOPA DECARBOXYLASE)🡪 concentration in synaptic vesicles
        + This enzyme is widely distributed in intestinal mucosa so NEED TO GIVE A DECARBOXYLASE INHIBITOR (want the levodopa to get to brain—1-3% of the dose gets into the CNS)

Adverse effects—CV system (tachy, arrhythmias), nausea

* + - * For this drug to be effective some nigrostriatal neurons must still be alive—effects will ↓ as disease progresses
      * Abs—effected by rate of gastric emptying and gastric pH
      * Worsening of sx’s near the end of the dose interval.
      * ON-OFF phenom—bradykinesia🡪 dyskinesia
      * Adverse: N/V, anorexia, SNS, Dyskinesias, Behavioral
      * Drug interaction—**MAOI🡪 HTN,** antipsychotic drugs (that block DA receptors--↓ levodopa effect), anticholinergic drugs
      * Inhibitors of COMT ↓ levodopa metabolism 🡪 on period lengthen (↑ drug effects)
    - **CARBIDOPA**
      * Inhibits the aromatic-L-amino acid decarbox—does NOT cross BBB
      * This is the one given w/ levodopa to prevent metabolism before it gets into the brain
  + **INHIBIT DA BREAKDOWN**
    - **SELEGILINE**
      * MAO-B INHIBITOR (blocks DA breakdown)
        + Nonselective MAOI + levodopa🡪life threatening
      * ↑ the CNS effects of levodopa (good and bad effects)
  + **POSYSYNAPTIC DA AGONIST**
    - **BROMOCRIPTINE**
      * DA-agonist
      * Also useful in Tx AMENORRHEA-GALACTORRHEA associated w/ hyperprolactinemia (prolactin secreting tumor)
        + Pituitary cells that release prolactin receive DA inhibition
    - **PRAMIPEXOLE & ROPINIROLE**
      * some selectivity for D2-like receptors (DA2 and DA3)
      * Alone or in combo w/ levodopa/carbidopa
      * Ropinirole is also approved for restless leg syndrome
      * Longer DOA than levodopa
      * Adverse: orthostatic hypotension, N/V, anorexia, dyskinesias, mental disturbances
  + **PROMOTE DA RELEASE**
    - **AMANTADINE**
      * Stimulate presyn release of DA
      * Used alone in early stages
      * Benefits are short lived
  + **DRUGS THAT INHIBIT CHOLINERGIC NEUROTRANSMISSION IN THE STRIATUM**
    - **BENZTROPINE**
      * Atropine-like but w/ better ration of CNS:PNS effects
      * Used for ANTIPSYCHOTIC DRUG –INDUCED PARKINSONISM
* **CNS STIMULANTS**
  + **METHYLXANTHINES**
    - Heart actions—positive inotropic and chronotropic effects (arrhythmias at ↑ doses)
    - Vessel-↓ R systemically, ↑ cerebral R
    - Diuresis, stimulate gastric acid secretion, metabolic effects (↑ BMR), skeletal muscle (↑ contractile strength at very high conc; ↓ doses for this if you have COPD)
    - Poor water solubility—abs slow
    - Demethylated in liver and oxidized
    - Readily penetrate BBB and placenta
    - **CAFFEINE**
      * Competitive ANTAGonists at ADENOSINE receptors—adenosine is inhibitory NT
      * ↑ doses—inhibit PDE
      * Effects: ↓ fatigue, ↓ reaction time, ↑ awareness of sensory stimuli, ↑ performance on some tasks, can stimulate respiration at ↑ doses
      * Adverse: nervousness, insomnia
      * Use: tx cerebrovascular HA (b/c in this the vascular is dilated and you want to ↑ R)
      * Widely abused
      * Dependence—HA, lethargy, irritability
    - **THEOPHYLLINE**
      * Used to tx asthma but narrow therapeutic index
      * Actions: diuresis
      * Adverse--convulsions are possible
      * Poor water solubility so inject (theophylline salts)
      * No tolerance to bronchial SM effects
  + **SYMPATHETOMIMMETICS**
    - **AMPHETAMINES—**release NE and DA
      * Substrate of DAT so competitively inhibits DA transport. In the cell it alters the VMAT and impedes the filling of synaptic vescicles🡪 cytoplasmic DA ↑ 🡪 reversal of DAT so expel DA🡪 ↑ extracellular DA
      * Actions: ↑ alertness, wakefulness, ↓ fatigue, ↓ distractibility, anorexia, euphoria, ↑ inner sense of well-being
      * Adverse: HTN, Tachy, premature beats, hyperactive DTR, tremor, weight lood
      * Tolerance—CNS actions some CV actions
      * High abuse liability associated w/ addiction and binge use (similar to cocaine) but little or no dependence
      * Medical Uses: ADHD, Narcolepsy, Weight Loss
      * **DEXTROAMPHETAMINE**
        + D-isomer 🡪 greater potency for CNS than PNS effects
      * **METHYLPHNEIDATE (RITALIN)**
        + Similar to Dextroamphetamine
    - **COCAINE**
      * Inibits DAT🡪 ↑ extracellular DA
        + Also inhibit reuptake of NE & 5-HT
      * Tox: CV—tachy, arrhythmias, angina, infarct, ICH, Seizures, obstetric complications (premature separation of the placenta), ENT findings (nasal ulceration)
      * High abuse liability associated w/ addiction, dependence is minimal
        + Craving for drug—dysphoria, psychic depression, sleepiness, fatigue, bradycardia
      * Base form—CRACK
      * Acid—SNORT FORM
* **ANTI-PSYCHOTICS**
  + THOR washed his CLOZs in CHLORox wearing nothing but a HALO...b/c, you know, he thought he was Thor but was really just a crazy naked schizo at the laundromat. (Thioridazine, Clozapine, Chlorpromazine, Haloperidol)
  + **Psychoses**: Schizophrenia, depression, bipolar disorder, schizo-affective, Korsakoff's syndrome, toxic psychosis (from amphetamines, phencyclidine, or steroids)
    - Korsakoff caused by a lack of thiamine (vitamin B1) in the brain. Linked to chronic alcohol abuse and/or severe malnutrition. There are 6 major sx: anterograde amnesia, retrograde amnesia, severe memory loss confabulation, (invented memories which are then taken as true due to gaps in memory sometimes associated with blackouts), meager content in conversation, lack of insight, apathy (the patients lose interest in things quickly and generally appear indifferent to change)
  + **Actions**
    - Work at 5-HT receptors, Muscarinic R, α adrenergic R, Histamine R, and of course DA receptor
    - Suppression of psychotic sx
      * b/c competitive antag of DA receptors on neurons receiving mesolimbic or mesocortical innervation
      * esp in pts w/ schizo (+ symptoms respond best; - symptoms respond less)
    - Acute neurotoxicities (extrapyramidal signs;EPS)—antagonistic effects of DA receptors in striatal neurons🡪 ↓ nigrostriatal transmission (parkinsonism)
      * Not seen in atypical/newer drugs
    - Tardive dyskinesia (oral and facial dyskinesias, choreoathetosis and/or dystonia)—late appearing dyskinesias. Takes months or years for this to appear!—seem like ↑ sensitivity to DA (↑ regulation of DA receptors after prolonged therapy)
      * DON'T LET THIS HAPPEN!
      * Rare w/ atypical drugs
    - Neuroleptic malignany sx—rare but fatal
      * Parkinsonism + catatonia, autonomic instability, hyperthermia and stupor
      * Tx: cooling, diazepam or dantolene
    - Atropine-like action: blockade of muscarinic receptors (dry mouth, dry skin, tachy, difficult urination)
    - Orthostatic hypotension—especially drugs that are strong blockers of α adrenergic receptors (chlorpromazine)—tolerance
    - Sedation—possibly b/c of block of H1 receptors
    - Endocrine effects—block of DA receptors in hypothalamus and pituitary—PROLACTIN SECRETION IS STIMULATED
    - Results—false positive pregnancy test, gynecomastia, galactorrhea, ↑/↓ libido
    - Sexual dysfunction in both men and women
    - Antiemetic effect—block of DA receptors in chemoreceptor trigger zone
    - Seizures--↓ threshold
    - Hypersensitivity rxn
    - Eye problems
    - Cardiac toxicities
    - 
  + **TYPICAL (FIRST-GENERATION): D2 RECEPTOR ANTAGONISTS**
    - **PHENOTHIAZINES**
      * **ALIPHATIC: CHLOROPROMAZINE**
        + Effect:
        + α-adrenergic receptor agonist activity🡪 hypotension
        + Antiemetic effect—block of DA receptors in chemoreceptor trigger zone
        + ↑ hypersensitivity rxns
      * **PIPERIDINE: THIORIDAZINE**
        + Not anti-emetic
        + ↑ doses can cause retinal deposits
        + ↑ doses associated w/ T wave and QT abnormalities and can produce fatal ventricular arrhythmias
      * **PIPERAZINE: FLUPHENAZINE**
        + Antiemetic effect—block of DA receptors in chemoreceptor trigger zone
    - **BUTYROPHENONES**
      * **HALOPERIDOL**
  + **ATYPICAL (SECOND-GENERATION): 5HT2 >D2 BLOCK**
    - These have fewer DA (DA4) receptors involved and only one kind of serotonin receptor (2A) is antagonized
    - 5-HT receptor role🡪 lead to weight gain
    - used to tx levodopa psychosis
    - ↑ blood sugar, ↑ lipids and cholesterol, ↑ weight gain
    - ↓ EPS and ↓ tardative dyskinesias
    - **INDOLES**
      * **CLOZAPINE**
        + ↑ frequency of Agranulocytes
      * **RISPERIDOL**
      * **ARIPIPRAZOLE**
  + **Drug interactions w/ Antipsychotics**
    - Additive CNS depression
    - Additive anticholinergic effect
    - Additive quinidine like effects on the heart (thioridazine)
    - Block effectiveness of levodopa in parkinson’s dz (less in newer drugs)
    - Block amphetamine psychosis
    - Seizure threshold is ↓ --danger for epileptics or in sedative-hypnotic or ethanol withdrawal
* **OPIOIDS**
  + **MORPHINE**
    - Opioid Receptors are g-protein coupled (mostly Gi/Go) and are located mostly in CNS and GIT
      * Presynaptic opioid receptors ↓ Ca conductance while postsynaptic opioid receptors ↑ K+ conductance
      * Subtypes:
        + **MU—(MORPHINE SITE OF ACTION AND MOST OTHER OPIOID ANALGESICS)**
        + **KAPPA—**PENTAZOCINE (THE KAPPAS HAVE A PENT HOUSE HAVE YOU ‘CINE’ IT??
        + **DELTA**
      * Opioid AGONISTS—inhibit the local circuit inhibitory neuron🡪 DISINHIBITS the INHIBITORY PAIN NEURON (so now the inhibitory pain neuron is active)
    - ACTIONS
      * Analgesia (↑ pain threshold, changes subjective response to pain)
      * Euphoria/Dysophoria—determined by expectation, route of admin, previous experience, presence of pain
      * ↓ anxiety
      * ↓ consciousness—dose dependent
        + ↓ doses—sedation (mental clouding)
        + ↑ doses—LOC, coma
      * Respiratory depression—↓ sensitivity to CO2 (↑ PaCO2, ↑ CBF). This is what kills you in OD
      * Cough Suppression (depresses cough reflex)
      * Constriction of pupils (miosis)
        + Hypoxemia causes dilation so if morphonine OD patient becomes hypoxic the pupils will be dilated
        + ↑ PSNS output to pupil
      * Truncal Rigidity—only seen in very high doses
      * N/V—activated chemoreceptor trigger zone, also a vestibular component
      * Cardiovascular—mild bradycardia, hypotension in OD or compromised C-V system patient, ↑ intracranial BF and ↑ CSF pressure, relieves dyspnea in pulmonary edema, ↑ histamine release (curare can also cause this)
      * GIT--↑ resting tone, ↓ peristalsis, ↓ secretions, ↓ sphincter tone-🡪 CONSTIPATION (may be limiting factor in tx patients)
      * ↑ biliary tone
      * GU tract--↓ renal function, ↑ ADH—transient ↓ in urine product, ↑ tone of ureter bladder and sphincter, prolonged labor
      * ↓ GnRH and CRH-🡪 ↓ in LH, FSH, ACTH and β-endorphin
      * ↑ prolactin and ADH
      * ↓ body temp
    - PHARMACOKINETICS
      * Liver is good at glucuronidating morphine to M-3-G
      * Large first-pass effect🡪 limited bioavailability
    - **SIMILAR DRUGS (**just differ in potency)**: OXYMORPHONE (more potent)**
    - May need to treat withdrawal w/ clonidine (↓ ANS)
      * 8-14 hrs—restless
      * 16-18 hrs—lacrimation, rhinorrhea, perspiration, yawning
      * 24 hrs—chills, gooseflesh, mescle cramps, mydriasis, mild HTN, hyperpnea, hyperthermia, twitches, involuntary kicking
      * 36 hrs—N/V/D gagging
      * 72 hrs—symptoms begin to stop
  + **ETROPHINE**
    - Imobilon—animal tranquilizer
    - 10000x’s more potent than morphine b/c 10000x’s more affinity for my receptors
  + **HEROIN (DIACETYLMORPHINE)**
    - Low affinity for mu receptor. It gets metabolized to monoacetylmorphine which has ↑ mu affinity—crosses BBB🡪 metabolized to morphine
    - 3-5x’s more potent than morphine
  + **CODEINE (3-METHOXY-MORPHINE)** 
    - 1/12th potency of morphine but EQUAL cough suppressant
    - Dysphoria w/ ↑ doses
    - 10% is converted to morphine🡪 analgesia
    - Polymorphism in CYP2D6
      * 10% resistant to codeine (not metabolized to morphine)
      * 5% get excessive response
  + **HYDROCODONE**
    - Metabolized to hydromorphone (morphine like) by CYP2D6
    - Hydromorphone may accumulate in patients w/ renal failure
    - Combo w/ acetaminophen (Vicoden)
  + **DEXTROMETHORPHAN**
    - Effective antitussive
    - NO analgesic
    - High doses can cause CNS effects
  + **MEPERIDINE (DEMEROL)**
    - Fast onset
    - Short DOA
    - Used in pregnancy or cleaning wounds!
    - Atropine like action (pupillary constriction)
    - Less constipation
    - No significant anti-tussive activity
    - Toxicity—respiratory distress, ↓ consciousness
    - Toxic due to metabolite—normeperidine🡪 CNS excitation, convulsions, delirium
    - INTERACTION W/ MAOI (fever, HTN, coma, severe respiratory depression)
  + **FENTANYL**
    - MU receptor agonist (80-100x’s morphine potency)
    - Short DOA b/c of distribution/redistribution
    - Used: IV analgesia and to reduce consciousness
      * Transdermal patch (FOR CANCER PATIENTS TO TX BREAKTHROUGH PAIN)**,** transmucosal formulation, transbuccal form
  + **METHADONE**
    - Slower biotransformation than morphine so it accumulates (so w/ repeated doses ↑ duration of analgesia) –long acting
    - Special uses: TREAT OPIOID ABUSE
      * Acute: substitute for usual drug then slowly reduce (avoid withdrawal sx)
      * Chronic: “maintence” programs. Sub it for usual drug then slowly RAISE dose to produce ↑ tolerance🡪 goal is to preclude any effect should the subject take an opioid agonist
  + **OXYCODONE**
    - more potent than codeine
    - metabolized to oxymorphone by CYP2D6—metabolite may accumulate in patients w/ renal failure
    - Time-release tablets (if you chew them you defeat the purpose)
  + **TRAMADOL**
    - Weak opioid agonist
    - Low analgesic efficacy
    - Action due to opioid receptor action & inhibition of SERT! (maybe also a little NET)
    - Size effect: SEIZURES
  + **D-PROPOXYPHENE (JUST KNOW NAME)**
    - Not used anymore
  + **ENDOGENOUS OPIOPEPTINS**
    - **MET-ENKEPHALIN**
      * Proenkephaline derived
      * Like a NT
    - **β-ENDORPHIN**
      * Pro-opiomelanocortin derived (POMC)
      * Acts like a hormone. Mostly in the pituitary and hypothalamus and released into bloodstream
  + **LOW PC, DON’T CROSS BBB**
    - **DIPHENOXYLATE**
      * Poor solubility, poor BBB penetration
      * Used to control diarrhea
      * Low abuse liability
    - **LOPERAMIDE (IMODIUM)**
      * Even Lower abuse liability
  + **OPIOID ANTAGONISTS**
    - **NALOXONE**
      * Competitive antagonist at ALL opioid receptors
      * W/ pts who are dependent will ppt an immediate withdrawal sx
      * No matter how much naloxone you use will just shift PCO2 toward normal when using it will morphine
      * Short DOA
      * First pass biotransformation—not effective orally
    - **NALTREXONE**
      * Oral and longer acting
    - **NALMEFENE** 
      * Longer-acting
  + **PARTIAL-MIXED AGONISTS/ANTAGONISTS**
    - **PENTAZOCINE**
      * Mixed agonist-antag
        + Kappa-agonist
        + Mu-antag
      * May ppt withdrawal (ANS hyperactivity)
        + May need to treat withdrawal w/ clonidine (↓ ANS)
      * ↑ dose you get kappa receptor response (dysphoric, psychotomimetric actions)
      * ↑ BP (so don't use in patients w/ heart problems)
    - **NALBUPHINE**
      * + Kappa-agonist
        + Mu-antag
    - **BUTORPHANOL**
      * + Kappa-agonist
        + Mu partial agonist
    - **BUPRENORPHINE**
      * + Kappa-antagonist
        + Mu partial agonist
      * Used in MAINTENANCE tx of heroine (must have the pt detox first)
        + It's a long acting drug

**ANTIDEPRESSANTS/ANTI-MANICS**

*Depression is thought to be related to ↓ NE and/or 5-HT neurotransmission*

*-Slow responses—changes in gene expression (use CREB, ↑ expression of BDNF)*

*-all drugs have delayed onset of therapeutic effects*

*-↑ incidence of suicide*

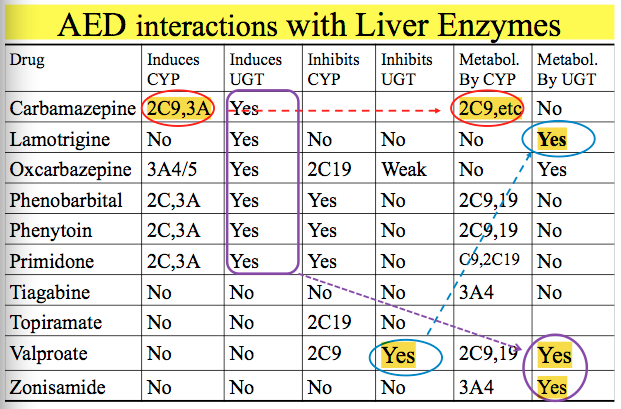
* **INHIBIT NE REUPTAKE 🡪 ↑ NE IN SYNAPTIC CLEFT**
  + *Other uses for amine reuptake inhibitors is –PTSD, OCD, Social anxiety disorder, generalized anxiety disorder, panic disorder, pain disorders, prementral dysphoric disorder (SSRI), smoking cessation, Bulimia (not anorexia), bed wetting*
  + **TRICYCLIC (1ST GENERATION)**
    - *The TCA’s lead to β and α2 receptor down regulation*
    - **AMITRIPTYLINE & NORTRIPTYLINE**
      * Inhibit NET and SERT
      * Antagonist at muscarinic receptors (look like atropine)
      * Act like local anesthetic-type antiarrhythmic (class1a)
      * α1-receptor antag
      * antagonists at H1 receptors (like old fashion antihistamine)
      * Cadiotoxic and lots of antimuscarinic effects
      * Sexual side effects
      * 1 week supply could be fatal
      * mostly long DOA
      * Start w/ low dose and ↑
      * Drug interactions—**MAOI,** fluoxetine (SSRI) inhibits the biotransformation of these
  + **ATYPICAL (2ND GENERATION)**
    - *NO INTERFERENCE W/ SEXUAL FUNCTION*
    - **BUPROPION—UNCICYCLIC**
      * Inhibits DAT (and NET a little) and releases presynaptic DA and NA
      * Adverse: insomnia, agitation, and anorexia
      * Approved for smoking sessation
      * LOWERS seizure threshold
    - **MIRTAZAPINE—TETRACYCLIC**
      * α2-antagonist (blocks the normal feedback mechanism) so NE and 5-HT release are ↑
      * also antagonist at other 5-HT receptors and H1 receptors so its quite SEDATING
  + **SEROTONIN-SELECTIVE REUPTAKE INHIBITORS (SSRIS)**
    - **FLUOXETINE—MANY DRUG INTERACTIONS!!!**
      * Metabolized to norfluoxetine (active) which has longer half-life so it accumulates
      * **STRONG CYP2D6 INHIBITOR (**this metabolizes TCA’s)
    - **SERTALINE—**short acting
    - **PAROXETINE**
      * **STRONG CYP2D6 INHIBITOR**
      * short acting
    - **CITALOPRAM**
    - All of these selective for SERT
    - No myocardial effects, much safer in OD
    - 1st drug tried in new patients
    - Adverse effects associated w/ ↑ 5-HT
      * N/D, GI upset, Impaired sexual function and interest (more than w/ TCA), HA, insomnia
      * Serotonin Syndrome—DANGEROUS (get it when you use w/ MAOI or OD on drug)
        + Altered mental status, sweating, fever, tremor, myoclonus
      * Discontinuation Syndrome—more obvious w/ shorter t1/2 like (sertraline and paroxetine)-🡪 dizziness and paresthesias
    - ↓ risk of suicide
  + **SEROTONIN-NONSELECTIVE REUPTAKE INHIBITOR (SNRI)**
    - **DULOXETINE**
    - **VENLAFAXINE**
      * Biotransformed to desvenlafaxine which is active
      * CARDIOTOXIC
    - Both inhibit SERT and NET
    - No direct cardiac tox
    - Safer than TCA in OD but venlafaxine has MORE CARDIOTOX than SSRI!
    - Adverse: ↑ HR and BP, insomnia, anxiety, discontinuation syndrome
    - ↓ risk of suicide
  + **5-HT ANATAGONIST**
    - **TRAZODONE—**not commonly used
    - **NEFAZODONE—**never used
    - Significant sedation—sometimes used an a hypnotic
  + **MAO INHIBITOR—***long acting, irreversible inhibitors!*
    - **SELEGILINE**
      * Used also in tx of Parkinson dz
      * Selective for MOA-B
      * Drug and food interactions is less of a problem
    - **TRANYLCYPROMINE**
    - Both are irreversible inhibitors. Slow TOA (requires resynthesis of enzyme)
    - Used in patients unresp. To other drugs
    - LOTS OF DRUG INTERACTIONS and FOOD INTERACTIONS
      * Drugs
        + OTC: Cold and cough meds, Nasal decongestants, Hay-fever meds, Sinus meds, Asthma inhalants, Anti-appetitite meds, Wt ↓ preps, L-tryptophan containing preps
        + Rx: Meperidine, buspirone (HTN) amitriptyline, nortriptyline, carbamazepine, cyclobenzaprine, TCA’s, SSRI’s, SNRI’s, tyramine (HTN crisis), levodopa (HTN crisis)
      * Food—liver, fava beans, sauerkraut, cheese, yogurt, beer and wine, chocolate, caffeine
    - Adverse: HA, drowsiness, wt gain, postural hypotension, sexual dysfunction, agitation and insomnia
    - OD: agitation, delirium, seizures, coma, shock, hyperthermia
    - Withdrawal rxn: axiety, sweating, HA
  + **MOOD STABILIZORS**
    - **LITHIUM**
      * Used for bipolar (manic), acute mania, and to prevent relapse of bipolar
      * Narrow therapeutic window
      * In the body it is handled like Na (excretion even depend on Na intake)--↓ Na intake🡪 serious toxicity
        + Any ↓ in Na will lead to Li+ accumulation (diuresis, diarrhea, dehydration)
      * Clearance is ↓ during pregnancy
      * 2-3 weeks until see effects
      * Mech: affects NE and 5-HT neurotransmission--↓ availability of IP3
      * Adverse: Tremor, polyuria and thirst (↓ kidney’s response to vasopressin🡪 nephrogenic diabetes insipidus. Responds to amiloride), edema, wt gain, fatigue, weakness, HA, confusion, memory impairment, ↓ thyroid function, ↓ SA node function, acne like skin eruptions, Leukocytosis (looks like infection but it isn’t), N/V anorexia
      * As levels ↑ 🡪 ECG changes (arrhythmias🡪 sudden death), hypotension, incoordination, course tremor, ataxia, tinnitus, minor seizure activity, generalized seizures, coma, DEATH
    - **VALPROIC ACID**
      * Liver toxic
    - **CARBAMAZEPINE**
      * Induces its own metabolism and the metabolism
* **ANTI-EPILEPTICS** (limit seizure spread)
  + *Epilepsy ↑ risk to fetus so tx pregnant women w/ epilepsy*
  + **NA+ CHANNEL BLOCKER ANTIEPILEPTICS**
    - **PHENYTOIN**
      * Partial, generalized tonic-clonic seizures (NOT absence)
      * Prolongs the time the voltage gated Na channel is in the inactivate state which makes the neurons refractory period longer🡪 limits ability to transmit series of AP’s
      * Slow abs from GIT—once absorbed HIGHLY PROTEIN BOUND (drug interactions)
      * Elim—met to inactive then its glucuronidated
        + ENZYMES IS EASILY SATURATED—goes from 1st order to 0 order (high conc.) –dose concentration curve is not linear.
      * Adverse: nystagmus, ataxia, vertigo, diplopia, sedation, others—Gingival hyperplasia, hirsutism, lymphadenopathy, ↓ vit D metabolism—bone malformation, periph neuropathy
      * Fetal hydantoin syndrome (all AED’s)
      * Interactions: drugs that are highly protein bound, competition for hepatic enzymes, induction of hepatic enzymes
    - **FOSPHENYTOIN**
      * --water soluble pro-drug for IV or IM use
      * Adverse--HYPOTENSION
    - **CARBAMAZEPINE**
      * Prolongs Na channel inactivation
      * Use: partial, generalized tonic-clonic (not absence), anti-manic, trigeminal neuralgia
      * INDUCES ITS OWN METABOLISM--↓ its own half life.
        + Also induce metabolism of other AED’s, oral contraceptive
        + Biotransformation of this drug is inhibited by grapefruit juice🡪 ↑ bioavailability
      * Adverse: dose related—ataxia, vertigo, diplopia, idiosyncratic reactions like aplastic anemia, agranulocytosis, skin rash
    - **VALPROIC ACID**
      * Inhibits Ca currents in thalamic, prolong Na channel inactivation, and affects synthesis and breakdown of GABA (not in humans)
      * Use: Absense, myoclonic epilespsy, generalized tonic-clonic (grand mal)
      * Also used to treat bipolar disorder (TWO WORDS so BI-polar) and as prophylaxis for migraines
      * 90% protein bound (drug interactions w/ warfarin)
        + displaces phenytoin from plasma proteins!!!
        + Inhibits metabolism of several drugs (phenytoin, carbamazepine, phenobarbital, lamotrigine)

B/c it inhibits CYP2C9

* + - * + Adverse: **NO SEDATION,** GI irritation, weight gain, tremor, hair loss, LIVER TOX/HEPATITIS in kids <2 and when used w/ other AEDs, TERATOGENIC
    - **LAMOTRIGINE (LA MOAT GAVE ME A RASH!!---STEVE IS A LAM-O)**
      * Adjunct in partial or generalized seizures, also used in absence epilepsy
      * Prolongs Na channel inactivation
        + and has some actions to some types of voltage-gated Ca channels
      * Adverse—LIFE THREATENING RASH!! –can progress to stevens johnsons syndrome
  + **ENHANCE GABA**
    - **BENZODIAZEPINES**
      * **CLONAZEPAM**
        + 2nd line drug for partial, absence, myoclonic seizures and infantile myoclonic spasms
        + Adverse: SEDATION and tolerance
      * **DIAZEPAM/LORAZEPAM**
        + STATUS EPILEPTICUS—emergency situation

Tx suspicion: Airway, breathing, circulation, Give drug IV, Benzo then follow w/ IV fosphenytoin

* + - * + Risk—too much effect—respiratory depression!
    - **BARBITURATES**
      * **PHENOBARBITAL**
        + Use: partial seizures, many generalized seizures (not absence)
        + ↑ GABA actions at GABAA
        + more selective AED than other barbituates
        + SEDATION is a problem
        + May see hyperactivity in kids
  + **T-TYPE CA2+ CHANNEL**
    - **ETHOSUXIMIDE—**TREVOR SUX AT MAKING UP MNEUMONICS
    - FOR ABSENSE SEIZURES
    - Inhibits T-type voltage gated Ca channels in thalamus
    - Adverse: GI distress, sedation (usually limited factor)
  + **INHIBIT EXCITATORY NT RELEASE**
    - **GABAPENTIN (Α2Δ)**
      * Use: partial seizures, generalized tonic-clinic seizures also post-herpetic neuralgia
      * Other uses: diabetic and other painful neuropathy
      * Mech: inhibit function of presynaptic voltage gated Ca channels--↓ release of glutamate
  + OTHER TX MODALITIES
    - Vagal N. stimulation
    - Ketogenic diet (high in fat, low in carbs and protein🡪 ketosis)
    - Surgical

****

* **SPASMOLYTIC DRUGS**
  + **BACLOFEN**—↑ inhibition
    - Antagonist at GABAB receptors🡪 ↑ K+ conductance🡪 hyperpol of the neuron
    - Adverse—sedation, withdrawal seizure
  + **DANTROLENE**—inhibit Ca release from ryanodine receptors on the SR
    - Used to tx malignany hyperthermia (using succinylcholine and halothane together)
    - Adverse: sedation and muscle weakness
  + **DIAZEPAM** 
    - Enhance GABAA effects at their receptors. Actions in SC as well as BS
  + **CYCLOBENZAPRINE**—alter descending tone
    - Significant anti-muscarinic effects
    - Adverse: sedation, confusion
  + **BOTULINUM TOXIN**—block Ach release from nerve terminals
* **DRUGS OF ABUSE**
  + **OPIOIDS**
  + **SEDATIVE-HYPNOTICS**
  + **ETHANOL**
  + **BENZODIAZEPINES**
  + **VOLATILE INTOXICANTS**
  + **AMPHETAMINE TYPE STIMULANTS**
  + **COCAINE**
  + **CAFFEINE**
  + **HALLUCINOGENS, PHENCYCLIDINE, MARIJUANA**
  + **NICOTINE**

**GI DRUGS MOST IMPORTANT DRUG NAMES TO REMEMBER**

* **CIMETIDINE**
  + H2 blocker, blocks met of drugs by P450 oxidases; antiandrogenic (galactorrhea in F, impotence & gynecomastia in men)
* **OMEPRAZOLE**
  + irreversible PPI, delivered to stomach via the blood, has either enteric coating or w/NaHCO3 to avoid activation in the stomach, oral or injected & used short & long term. Worries: cancer of ECL cells? & higher pH allowing bacterial growth, hypoMg, fractures. Inhibits CYP2C19 & 3A4 so blocks Diazepam & Clopidogrel. Drug interactions due to higher pH🡪 less keoconaole, Fe salts, ampicillin, atazanavir & more Digoxin
* **MISOPROSTOL**
  + Prostaglandin E2 derivative. Increases blood flow, mucous and decreased acid. SE= diarrhea & uterine contraction. Contraindicated in pregnancy!
* **SUCRALFATE**
  + polymerizes pH<4 so coats for 6 hours.Interacts w/absorption of drugs: Cimetidine, Omeprazole, Tetracyclines & antacids contraindicated for 30 min after
* **BISMUTH SUBSALICYLATE** 
  + precipitates if pH<4 so coats ulcer & kills H.pylori
* **MAGNESIUM AND ALUMINUM HYDROXIDE**
  + Antacids; Mg increases motility (diarrhea) & Al decreases motility (constipation) so they’re often mixed.Ca,Mg,Al inhibit absorption of tetracyclines & quinolones. Causes gastric pH to rise. And watch for cation toxicity if renal fxn is impaired.
* **TETRACYCLINE, METRONIDAZOLE**
  + antibiotics. H pylori becomes R to metrodinazole & clarithromycin so use more 2 or more
* **MAGNESIUM HYDROXIDE** 
  + Antacid reacts quickly at pH 8-9
* **MgSO4** 
  + osmotic fast acting laxative. Works in 1-3 hrs. Can cause Mg toxicity if renal fxn impaired. Can be used for drug overdose.
* **SORBITOL** 
  + Osmotic fast acting laxative. Can be used for drug overdose
* **PSYLLIUM**
  + A Fiber; binds water to reduce watery stool & create distention to improve gastric motility; binds Digoxin & warfarin. Lowers cholesterol by binding bile acids.
* **PHENOLPHTHALEIN**
  + Stimulant laxative works in colon due to enterohepatic cycling of glucuronides. Effects seen 6-8 hours. Withdrawn from market due to tumors in rats. Can cause hypoK.
* **BISACODYL**
  + Stimulant laxative works in the colon due to enterohepatic cycling of glucoronides and acts within 6-8 hours. Can’t chew or crush or will vomit. Can cause hypokalemia. Chronic use NOT recommended. Secreted in saliva, breast milk, urine.
* **SENNA**
  + Stimulant laxative that contains danthron glycosides and act in the colon. Secreted in saliva/breast milk/urine.
* **DOCUSATE**
  + Stool softener (lubricant, emulsifier, detergent). Mild laxation produced in 1-3 days.
* **CASTOR OIL**
  + Ricinoleic acid causes peristalsis/secretion of SI & colon. Complete emptying! NOT recommended for common constipation! Induce uterine contraction in pregnant women.
* **CISAPRIDE** 
  + 5-HT4 Receptor agonist used for GERD, diabetic gastroparesis, chronic constipation. Causes arrhythmias bc oxidized by CYP3A4 so don’t take with CYP inhibitor.
* **METOCLOPRAMIDE**
  + agonist at 5-HT4 receptors & antagonist at D2 & 5-HT3 receptors. Used for GI motility for gastroparesis, GERD and as anti-nausea to prevent N/V associated with chemotherapy. Serious side effect = Tardive dyskinesia.
* **DICYCLOMINE** 
  + Antimuscarinic used for IBS. Decreases motility. Don’t use if patient has GERD, UC, or glaucoma.
* **DIPHENOXYLATE AND LOPERAMIDE**
  + Opiod agonists that inhibit Ach release in the myenteric plexues. Decreases motility but increases GI muscle tone especially sphincters. Diphenoxylate- At typical doses no analgesia or euphoria. Higher doses can be so mixed. with atropine to limit abuse potential. Loperamide- Pumped out of the CNS so no analgesia/euphoria. Contraindicated for UC b/c may precipitate toxic megacolon.
* **PROCHLORPERAZINE**
  + ANTIemetic. Antagonist at D2,M, H1, 5-HT receptors. Reserved for when N/V is resistant to other drugs. Side effects due to dopamine antagonism (parkinsonism.)
* **SYRUP OF IPECAC**
  + Induces vomiting after drug overdose by acting in intestines & CTZ. Toxic doses damage liver, kidney, heart, & skeletal muscle. Chronic abuse cause CHF/myopathy.
* **ONDANSETRON**
  + Antagonist at 5-HT3 receptors. Effective in treating acute vomiting.
* **SCOPOLAMINE**
  + Antimuscarinic used for prophylaxis of motion sickness (most efficacious).
* **DIPHENHYDRAMINE AND DIMENHYDRINATE**
  + Antimuscarinic & antihistamine effects contribute to prevention of motion sickness. Sedative and anti-muscarinic effects.
* **PROMETHAZINE**
  + M & H1 antagonist. Prevents N/V in surgery. Prevents motion sickness. Has sedative & antimuscarinic side effects. Can cause respiratory depression so contraindicated in kids under 2. Can cause potential limb loss if into the artery.
* **MECLIZINE**
  + Antihistamine that produces less sedation and used for milder cases of motion sickness.
* **SULFASALAZINE**
  + Treatment of UC, CD, and RA. Prodrug cleaved by bacteria in the gut to become active 5-ASA which inhibits COX-2 and 5-lipoxygenase.
* **BALSALAZIDE**,
  + Newer prodrug taken orally that releases 5-ASA and cleaved by bacteria. Better than sulfasalazine for CD and used for mild-moderate UC. Better tolerated, fewer side effects.
* **MESALAMINE OR 5-AMINOSALICYLATE (5-ASA)** 
  + Active ingredient in sulfalazine & balsalazine; Indication UC. Oral or rectal use suppositories. Inhibits COX-2 and 5-lipoxygenase
* **CROMOLYN SODIUM**
  + prevents activation of mast cells. Treats UC and systemic mastocytosis.
* **INFLIXIMAB** 
  + Chimeric human-mouse monoclonal Ab to TNFa. Used with methotrexate. Treats moderate-severe Crohn’s and UC that’s unresponsive. Expensive!
* **PREDNISONE**- systemic GC; treating acute CD exacerbations. Don’t use for maintenance due to SE.
* **PREDNISOLONE**- systemic GC; treating acute CD exacerbations. Don’t use for maintenance due to SE.
* **BUDESONIDE**-
  + GC with high topical activity for mild-moderate CD. Also treats asthma. High first pass metabolism. Enteric coated and delayed release formulation to retain in gut until distal ileum and ascending colon. Much variability in “delay” of action.

**DIABETES DRUGS MOST IMPORTANT DRUG NAMES TO REMEMBER**

* **INSULIN LISPRO**
  + Ultra short acting insulin
  + B/c the amino acid sequence on the B-chain of this insulin has 2 AA switched it inhibits formation of hexameras w/ Zn so no dissociation necessary
  + OOA—5-15 min; PPC—30-90 min; DOA—3-4 hr
    - Should be administered 0-15 min before a meal (less time than regular insulin)
    - Disappears faster so ↓ risk of hypoglycemia
  + Soluble so can be give IV---solution has a pH <4
* **REGULAR INSULIN (HUMULIN)**
  + Short acting insulin
  + Zn2+ insulin solution
  + Released moderately quickly from SC sites
  + OOA—30 min PPC—1-2 hr DOA 5-8 hr
    - Administer 30-60 min before eating!
  + ONLY TYPE THAT CAN BE ADMINISTERED IV/IM in an emergency situation (diabetic coma)—must be in solution when you inject it
* **NPH INSULIN/ISOPHANE INSULIN** 
  + Intermediate acting insulin—administered SC
  + Suspension of crystal zinc insulin combined with 1 protamine (+) charge—so this is not in solution
  + MAY BE MIXED WITH REGULAR INSULIN—b/c it wont effect the absorption of the regular insulin
  + No useful in emergency situations
  + Slow absorption b/c it is a suspension so
    - OOA—2-4 hr; PPC—6-12 hr; DOA—16-24 hrs
* **INSULIN** **GLARGINE**
  + Long acting insulin
  + Modified human insulin—its not soluble unless the pH is <4; forms microppt at pH 7 after SC injection
  + Contains Zn2+
  + Zero order absorption
    - Administered once daily at bedtime—to provide low levels of insulin during period of long fasting (sleep)
  + OOA—2-3 hr; PPC—no peak but plateaus; DOA—24+ hrs
  + DO NOT MIX WITH OTHER INSULINS—lispro solution is at a pH <4
* **TOLBUTAMIDE**
  + 1st generation Sulfonylureas (K+ channel blocker)
  + Blocks the K channel which causes depolarization of the PM which causes Ca channel to open and insulin gets released—DON'T NEED GLUCOSE TO FOR THIS DRUG TO STIMUALTE INSULIN (risk for hypoglycemia)
  + \*\*remember drugs that open K channels (Diazoxide, minoxidil, and HCTZ) all can lead to hyperglycemia b/c ↓ release of insulin
  + shortest t1/2 life of these—5 hrs; SAFEST in elderly patients
* **GLYBURIDE**
  + 2nd generation Sulfonylureas (K+ channel blocker)
  + t ½ is 10 hrs
  + more potent
* **REPAGLINIDE**
  + Is a meglitinide
  + Binds to the sulfonylurea receptor (at a different site than the sulfonylureas) and blocks the K channel🡪 stimulates release of insulin
  + Rapid OOA and short DOA (t1/2 1hr)
  + Administered 3-4x’s per day before each meal—mimics physiological insulin profile
* \*\*\*\*Tolbutamide, Glyburide and Repaglinide—all exhibit tachyphylaxis
  + Resistance to these drugs can develop maybe b/c as the disease progresses ↓ # of β cells (↓ insulin), ↓ muscle mass (↓ glucose uptake ability), ↓ physical activity (↓ glucose transporters in skeletal muscle)
* **GLUCAGON**
  + Can be used to treat severe hypoglycemia
  + Administer SC, IV, IM—follow it with carbs
  + Effects are not blocked by β blockers (EPI effects are)
  + Limitation—glucose stores must be available so not useful in starved patients. Less effective in type 1 than type 2 DM
* **METFORMIN**
  + It is a biguanide
  + Promotes action of insulin (especially in the liver—INHIBITS HEPATIC GLUCONEOGENESIS) and ↑ peripheral glucose uptake
  + DOES NOT induce insulin release (ONLY USED IN TYPE 2/INSULIN RESISTANT DM)
  + Administer w/ meals b/c need insulin and glucose to work
  + ↓ fasting hyperglycemia, ↓ post-prandial hyperglycemia, and rarely induces hypoglycemia
  + can be combined w/ sulfonylureas, acarbose, glitazones
  + KIDNEY ELIMINATION (very water soluble)—DM and elderly are most common ppl to have ↓ renal function so in patients w/ impaired kidney function this drug can accumulate and ↑ side effects which are transient N/V/D, weight loss ☺, impair vit B12 and folate absorption (rarely leads to pernicious anemia), LACTIC ACIDOSIS (so monitor renal function while on this drug can it can lead to this if its not cleared)
  + Drug interactions—cationic drugs, IV iodinated contrast materials like those used in urogrames, cholangiography, angiography, CT b/c they impair kidney function
  + Surgical procedures ↓ renal function so suspend metformin therapy and resume when the patients renal function is back to normal
  + Contraindications—CHF or MI (hypoxic states—b/c these states promote lactic acidosis), Liver disease (important for lactate metabolism), excessive alcoholism (potentiates effect on metformin on lactate metabolism)
* **ROSIGLITAZONE**
  + It is a thiazolidinediones
  + Used for type 2 DM
  + AGONIST FOR PPAR γ –regulates synthesis of insulin-responsive genes (↓ lipolysis, ↑ glu uptake, ↑ glu utilization)
  + REQUIRES INSULIN and PROMOTES INSULIN ACTIONS IN ADIPOSE TISSUE AND MUSCLE—works at diff sites than metformin so you can combine the two
  + LIPID SOLUBLE SO EXTENSIVE METABOLISM BY THE LIVER –monitor liver enzymes b/c may become toxic to the liver
  + Takes hours to see effects—administered 1-2x’s per day INDEPENDENT OF MEALS
  + ↓ fasting hyperglycemia, ↓ post-prandial hyperglycemia, and rarely induces hypoglycemia
  + Side effects—WEIGHT GAIN ☹--if used with metformin can counteract this some but not all the way, also causes edema, liver toxicity, risk of fractures in women, HEART FAILURE
  + Adverse effects of just rosiglitazone—CARDIAC ISCHEMIA, ANGINA, MI
  + Label now says that patients that are already on this can stay on this but it shouldn't be newly prescribed unless blood glucose can be controlled and patient doesn't want to be on piolglitazone (b/c ↑ risk of bladder CA)
* **ACARBOSE**
  + α glucosidase inhibitor
  + TYPE 2 DM
  + Competitive inhibition of α-disaccharidases in proximal small intestine
    - Slows down abs of most carbs
  + ↓ post-prandial hyperglycemia by 45-60
  + NO HYPOGLYCEMIA when used alone but can be used w/ sulfonylureas
  + ADMINISTED AT THE START OF A MEAL
  + Side effects—flatuelence, diarrhea, small weight loss
  + Contraindication—IBD
  + Metabolized in the GI tract and eliminated in feces
* **PRAMLINTIDE**
  + Analog of amylin (amylin is also released from β cells along with insulin)
  + Good for patients w/ type II DM
  + Inhibits post-prandial glucagon secretion
  + slow down gastric emptying, ↓ rise in blood glucose, inhibits glucagon release, ↓ appetite by working in CNS
  + NET: glucose enters blood more slowly
  + Used to improve glycemic control in patient who have failed to achieve desired glucose control
  + SC injection prior to major meal with short acting insulin (BUT DO NOT MIX b/c pH of this is acidic)
  + Effects: ↓ plasma glucose fluctuations (can produce severe hypoglycemia so don't use if you have “hypoglycemia unawareness”), ↓ HbA1C, ↓ weight, **↓ required dose of insulin**
* **EXENTAIDE**
  + GLP-1 like peptide (found in venom of Gila monster)
  + Stimulates insulin and amylin release but need glucose for it to work b/c need the ATP to close the K channel and depolarize the cell and open Ca channels
  + TYPE 2 DM ONLY
  + ↓ postprandial and fasting plasma glucose
  + Inhibits glucagon, slows stomach emptying, ↓ appetite via CNS
  + Side effects—N/V/D, ↑ hypoglycemia risk if used w/ sulfonylurea
  + Potential problems—ACUTE PANCREATITIS, ↓ RENAL FUNCTION
* **SITAGLIPTIN**
  + Inhibit dipeptidyl peptidase -4 (DDP-4)
    - Inhibits inactivation of incretins GLP-1 and GIP so increases GLP-1 and GIP in the blood 2-3 fold
  + Glucose-dependent stimulation of insulin
  + TYPE 2 DM
    - To improve glycemic control, monotherapy adjunct to diet and exercise, combo w/ metformin
  + ELMINATED BY KIDNEY (like metformin)—so dose is adjusted according to kidney function
  + POTENTIAL PROBS—ACUTE PANCREATITS

**ANDRENAL DRUGS**

* **PREDNISONE—**short acting GC; not active—must go to liver and get activated into prednisolone; has 4x’s antiinflamm activity of cortisol by only 0.3x’s its mineralcorticoid activity. No topical activity. Given orally
* **PREDNISOLONE** –Same actions as prednisone but can be used topical
* **TRIAMCINOLONE—**intermediate acting GC; Has 5x cortisol topical activity. No salt retaining ability. Can convert it into **ACETONIDE** and its topical activity goes up to 100x’s cortisols (beneficial in tx of asthma)
* **DEXAMETHASONE—**long acting GC; This drug is so potent so ↑ risk for side effects. Use these for cerebral edema (child w/ seat belt on gets in MVA w/ head trauma🡪 ↑ inflammation and swelling in the head so give this to tx the inflammation and not increase BP.
* **FLUDROCORTISONE—**mineralcorticoid; 250x’s aldosterones salt retaining ability.
* **COMPLICATIONS AND WHAT TO TREAT WITH:**
* **REPLACEMENT THERAPY** (adrenal insufficiency)
  + Hydrocortisone & Fludrocortisone
* **PALLITATIVE THERAPY**
  + ARTHRITIS AND TENDINITIS—Prednisolone
  + ALLERGY AND ASTHMA—Triamcinoone acetonide, Budesonide, Gluticason
  + DERMATOLOGICAL DISORDERS—topical ones
  + AUTOIMMUNITY—oral prednisone
  + ORGAN TRASPLANTATION—prdnisone & cyclosporine
  + MALIGNANCIES—prednisone
  + PREMATURE BIRTH--↑ surfactant w/ GC
  + GI DISORDERS
  + CEREBRAL EDEMA—Dexamethasone
  + HYPERCALCEMIC
  + SHOCK
  + COLLAGEN VASCULAR DISORDER
  + NEUROMUSCULAR DISORDERS
  + RENAL DISEASES
  + HEMATOLOGICAL DISORDERS

**ANTI-ADRENOCORTICOSTEROIDS**—useful in tx of disease of adrenal hyperactivity (Cushing, Conn)

* **INHIBITORS OF ADRENAL STEROID BIOSYNTHESIS**
  + **AMINOGLUTETHIMIDE**—inhibits conversion of cholesterion to 20-α-hydroxycholesterol; blocks production of all steroids from adrenal cortex
    - Used as adjunct in cushing, used to tx breast and prostate cancer (↓ estrogen)
  + **MEYRAPONE**—inhibits 11-β-hydroxylation of steroids
    - Blocks aldosterone and cortisol
    - Used as adjunct in cushing and to test pituitary ability to respond to ↓ levels of GC’s
* **ANTAGONIST**
  + **SPIRONOLACONE**—competitive antagonist to both mineralcorticoid and androgen recepotrs
    - Used as diuretic, to tx hirsutism, Conn’s
    - Cause hyponatremia/hyperkalemia, metabolic acidosis, gynecomastia, impotence
  + **EPLERENONE**—aldosterone antagonist
  + **RU486 (MIFEPRISTONE)—**anti progesterone and also potent anti-GC
    - Used in Cushing sx

**THYROID DRUGS**

**DRUGS FOR HYPOTHYROIDISM**

* **POWDERED THRYOID GLAND—**cheap, difficult to control, hypersensitivity rxns,
* **LEVOTHYROXINE SODIUM—**synthetic T4; Allergies can be developed to the filler, only once daily dosing. DOC
* **LIOTHYRONINE SODIUM—**pure T3; if patient presents w/ myxedema coma use this; THIS IS POTENT. CARDIOTOXIC
* **LIOTRIX—**4:1 T4:T3;

**DRUGS FOR HYPERTHYROIDISM**

* **THIONAMIDES—**Propylthiouracil (PTU), Methimazole, Carbimazole (10x’s more potent than PTU)
  + **INHIBITS THYROID PEROXIDASE**—block tyrosine iodination on TGB, block iodotyrosine coupling, PTU block deiodination of T4🡪T3
  + PTU needs multiple daily dosing; methimazole one need once a day. These do not block the release of thyroid hormone. Takes weeks to see ↓ in thyroid hormone.
  + Side effects: rashes, fever, vasculitis, arthralgia, cholestatic jaundice, hepatitis; hypothyroidism w/ prolonged or excessive tx
    - ↑ incidence of liver failure w/ PTU.
  + Advantage—avoids surgery and reversible; Disadv--↑ incidence of relapse and remission takes years.
  + Methimazole is first line drug for young patients w/ mild—moderate dz
  + PTU is second ling drug therapy unless the patients are allergic or intolerant to methimazole
  + Used as adjuncts to surgical removal or radioactive ablation of hyperthyroid gland to normalize the patient
* **IONIC INHIBITORS**
  + Thiocyanate (SCN-)—blocks the uptake of iodide
  + Perchlorate (ClO4)—blocks uptake of iodide—now is a dx agent for thyroid function
* **IODIDE—**inhibits TH synthesis and release—often used along w/ β blockers to tx thyroid storm. ↓ size and vascularity of thyroid gland. Rapid action. No used for long term.
* **RADIOACTIVE IODINE—**131—only isotope used to tx hyperthyroidism. 123 is used in clinical dx.
  + Effect—necrosis of follicle cells
  + Adv—only thyroid is effected, surfery avoided, inexpensive.
  + Disadvantage--↑ incidence of delayed hypothyroidism; potential carcinogen; crosses placenta SO FEMALE CANT BE PREGS. Can obliterate parathyroid gland b/c proximity to thyroid gland.

**DRUG NAMES To Know/Recognize IN PREGNANCY LECTURE**

* **OXYTOCICS – Drugs that contract uterine SM muscle**
  + **PROSTAGLANDINS**
    - **DINOPROSTONE**
      * PGE2. In cervix, relaxes SM muscle and stimulates collagenase. In uterus, induces contractions. Augments oxytocin effects so therapy should be stopped prior to administration of oxytocin. SE: Increased GI motility (NVD), hyperstimulation of uterus. Also used in 2nd trimester abortions.
    - **MISOPROSTOL**
      * PGE1 derivative. Used off label for cervical ripening. Advantages: more effective, faster, less need for oxytocin. A lot cheaper than the dinoprostone drugs. Dis: higher incidence of uterine hyperstimulation
    - **CARBOPROST**
      * 15-Me-PGF2a used to inhibit post-partum bleeding when oxytocin or methylergonovine fail. Contracts uterine SM muscle and also causes vasoconstriction. SE: GI (NVD), fever, increased BP and bronchoconstriction. Also used in 2nd trimester abortions.
  + **OXYTOCIN**
    - Acts on G protein-linked receptors that elevate Ca in uterine SM muscle and increases local prostaglandin production. Given IV, IM, or nasally (inactive orally). Short plasma half-life.
    - ↑ force, frequency, and duration of uterine SM muscle contraction, w/ normal relaxation. Sensitivity starts low, but increases throughout pregnancy (30x receptor increase)
    - Contracts myoepithelial cells around mammary alveoli as a result of suckling reflex
    - Weak antidiuretic and vasopressor activity (acts at ADH V2 and V1 receptors)
    - Used in induction of labor when 1.) Pregnancy gone beyond 42 weeks or 2.) When early vaginal delivery will decrease mortality or morbidity for mother or baby (usually bc of premature rupture of membranes). Contraindicated with: cephalopelvic disproportion, abnormal fetal presentation, previous uterine surgery, placental abnormality, umbilical prolapse, fetal distress. Before induction ensure fetal lung maturity and cervical ripening with glucocorticoids and prostaglandins.
    - Maternal monitoring: monitor BP, HR and uterine contractions during infusion
      * Stop if resting uterine pressure > 15-20mmHg, contraction duration >1min, or contraction frequency > 1 per 2-3 min
    - Fetal monitoring: monitor HR and rhythm.
    - Other uses: augment dysfunctional labor, control post-partum hemorrhage, promote milk ejection.
      * Oxytocin challenge test: temporarily decreases fetal blood supply. If fetus healthy, no change in HR. If not healthy, fetal HR decreases
    - Toxicity: uterine rupture, water intoxication
  + **ERGOT ALKALOIDS –** can get ergot poisoning due to prolonged vasospasm (ischemic pain and gangrene of feet, legs, hands and arms. Also dementia with hallucinations and uterine SM muscle contraction 🡪 abortion). Act at alpha adrenergic receptors, DA receptors, and Serotonin (5-HT) receptors (5-HT1A, 5-HT1D, 5-HT2)
    - ***Amine ergot alkaloids (ERGONOVINE and METHYLERGONOVINE)*** importation for effects on uterus. Rapid GI absorption and metabolism
      * Partial alpha adrenergic agonist and 5-HT2 agonist. Strong and prolonged contractions of uterus. Lower doses ↑ force and frequency of contractions with normal relaxation. With higher dose, force and resting tone increase with sustained contractions possible.
      * Less toxic that peptide alkaloids. Primarily used **postpartum** to assist involution and decrease hemorrhage
      * Use limited to a max of 1 week. May be given oral, IM, or IV.
      * SE: rare with IM or oral. Hypertension, nausea and vomiting (CTZ, GI), numbness and tingling of fingers/toes. Prolonged use results in “ergotism:” respiratory depression, hypothermia, convulsions, coma. Prolonged vasospasm leads to gangrene.
    - ***Peptide ergot alkaloids (ERGOTAMINE and DIHYDROERGOTAMINE (DHE))*** important in tx of hyperprolactinemia and migraine (best if given during prodrome). Poor GI absorption and slower metabolism 🡪 longer duration of action.
      * Agonist at presynaptic 5-HT1D receptors (decrease cAMP) on trigeminal nerves innervating cranial blood vessels, inhibiting release of inflammatory/vasodilator peptides (CGRP, substance P). Agonist at cranial vascular SM 5-HT1D receptors
      * Oral, sublingual, rectal, nasal, IV, IM.
      * SE: Nausea/vomiting (metoclopramide used as adjunct), potent vasoconstrictor with prolonged action (numbess,tingling, hypertension, coronary vasospasm, cumulative vasoconstriction with each dose)
      * Contraindications: CAD, PAD, HTN, elevated cholesterol, diabetes, pregnancy (cat X), hemiplegic or basilar membrane. Interacts with CYP3A4 (black box warning): ritonavir, erythromycin, etc can elevate plasma levels 🡪 cerebral or peripheral ischemia.
* **SUMATRIPTAN –** first line drug used for migraine with or without aura.
  + Selective agonist at 5-HT1D receptors on cranial vascular SM and presynaptic membranes. Little effect on arterial BP or PVR.
  + Not used for prophylactic therapy. Bioavailability 15% due to first pass effect (metabolized by MAO-A).
  + Interactions with MAO-Is, **SSRIs (serotonin syndrome)**, ergot derivatives. Pregnancy cat C (avoid use)
  + SE: unpleasant chest sx (heavy arms, chest pressure – not dangerous due to vaso/bronchoconstriction and muscle spasm). Vasospasm of arteries – can cause coronary vasospasm (contraindicated in pts with CAD)
  + Sumatriptan works faster than dihydroergotamine but there is a higher incidence of migraine recurrence
* **BROMOCRIPTINE –** selective D2 agonist (decreases cAMP)
  + Used for tx of
    - **hyperprolactinemia** (acts in ant pit)
      * suppresses galactorrhea, can induce regression of tumor
    - acromegaly (lowers GH 50%)
    - parkinson’s (acts in c. striatum)
  + SE: Nausea, GI sx, headache, dizziness, orthostatic hypotension. Give with food to minimize NV
* **DEXAMETHASONE AND BETAMETHASON**E
  + Glucocorticoids given between weeks 24-34 to promote surfactant production by type II pneumocytes. Stimulates synthesis of fibroblast pneumocyte factor. Last dose should be given >24 hours but <7 days before delivery
* **TOCOLYTICCS –** suppress premature labor and delivery
  + **MAGNESIUM SULFATE**
    - Tocolytic drug of choice due to low risk of SE and low cost.
    - May act as a Ca antagonist. Inhibits Ach release at uterine NMJs. High concentrations able to inhibit skeletal muscle NMJs leading to weakness, respiratory, and cardiac arrest. 100% renal elimination.
    - SE: transient hypotension and dry mouth. **Pulmonary edema** that could be fatal. Paralytic ileus, somnolence, paralysis.
    - Need to monitor: Mg levels, deep tendon reflexes, renal function (to detect fluid retention, which ↑ risk of pulmonary edema). Mg crosses placenta so newborn may have hypotonia and sleepiness that persists for several days (kidney function not yet fully developed)
    - Contraindications: myasthenia gravis, renal failure, hypocalcemia (intensifies effect of Mg)
    - Calcium gluconate used to treat toxicity
  + **TERBUTALINE AND RITODRINE**
    - B2 selective adrenergic agonists.
    - Major use is tocoloysis. Also used in prophylaxis and tx of acute asthma attack.
    - Oral and IV admin
    - SE: cardiac stimulation
  + **NIFEDIPINE**
    - Tocolytic. Ca channel blocker in SM muscle including uterus.
    - Maternal SE: vasodilation leading to tachycardia, hypotension, facial flushing, HA, dizziness, nausea.
  + **INDOMETHACIN**
    - NSAID (blocks uterine PG synthesis)
    - 2nd line tocolyic
    - Maternal SE: nausea, gastric irritation, interstitial nephritis, increased post-partum bleeding
    - Neonatal SE: renal failure, broncho-pulmonary dysplasia, **respiratory distress syndrome, premature closure of d arteriosus**, necrotizing enterocolitis, intracerebral hemorrhage
* **METHYLDOPA**
  + Drug of choice for treatment of chronic hypertension during pregnancy. Little effect on uteroplacental flow or fetal hemodynamics
  + Competes with DOPA and DA, NE, and EPI synthesis – produces Me-DA and Me-NE in brain
    - Me-NE is an alpha2 agonist that inhibits SNS outflow to vascular SM and heart**.** Also an α1 agonist, so does not block vasoconstriction or baroreflex completely
  + SE: may lead to sedation and increased prolactin
* **DRUGS FOR SEVERE PRE-ECLAMPSIA (>180/110) –** requires tx if immediate delivery not chosen. Need to lower BP and prevent seizures
  + **HYDRALAZINE (IV or IM) and LABETALOL (IV)**
    - Often used in combination
    - Hydralazine = vasodilator
    - Labetalol = beta blocker that also blocks alpha receptors

**DRUG NAMES TO REMEMBER /RECOGNIZE IN NSAID LECTURE**

* **NSAIDs in general:**
  + NSAIDs inhibit prostaglandin synthesis by inhibiting cyclooxygenase mediated conversion of arachidonic acid to PGH2. Salicylates also play role in NF-KB signaling in inflammatory cascade.
  + Uses:
    - treatment of pain-analgesia (block nerve sensitization by PGE2 and PGI2 for pain that is mild to moderate, ie muscle ache, headache, nerve ache etc. not useful for pain induced by exogenous prostaglandins; differ from opioids no tolerance/dependence and have a ceiling effect; can be used w/ opiods).
    - Treatment of fever – antipyresis (block PGE2 from acting on hypothalamus to change set point of temperature (no effect on normal temp, no effect on temp elevated by exercise ie hyperthermia, no effect on temp elevated by exogenous PGs).
    - Treatment of inflammation in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (although higher doses aspirin needed to treat inflammation more than for simple analgesia because more than just inhibiting COX2 is involved).
    - Modulation of blood clotting/thrombosis (low doses of aspirin rapidly and irreversibly inhibit platelet TXA2 synthesis by COX1 of platelets, which is needed for aggregation; does NOT block thrombin induced aggregation) so therefore prevents heart attacks and strokes.
    - Close patent ductus arteriosus (PGs needed to keep open. Use indomethacin to close)
    - Tocolysis. Use indomethacin to block PGs from inducing labor (not DOC for this, MgSO4 pref)
  + Adverse effects:
    - GI: bleeding, gastric and duodenal ulcers (since PGE2 protects mucosa)
    - Kidney: can induce kidney failure
    - Reye’s syndrome: hepatic and brain damage when kids take salicylates/aspirin when have influenza or chicken pox (mech unknown, so salicylates gen not used in kids)
    - Uric acid secretion: low 1-2g/d of salicylates DECREASE uric acid secretion by blocking active tubular secretion in kidney. High doses >5g/d of salicylates INCREASE uric acid secretion by stimulate uric acid secretion and block reabsorption. Intermediate dose (2-3g/d) no effect. All doses block probenecid which ↑ uric acid secretion.
    - Close ductus arteriosus; problem in last weeks of pregnancy
    - Hypersensitivity: can produce anaphylactic response esp if have asthma/nasal polyps. Tx w/ epinephrine
  + Toxicity of salicylates:
    - Early stage (35-50mg/dL):
      * CNS: tinnitus, hearing loss, vertigo, emesis (CTZ) resulting in fluid loss
      * Metabolic: uncouple mitochondrial ox phos->higher CO2 production, incr respiration and fluid loss
    - mild-moderate tox (50-80 mg/dL)
      * CNS: hyperventilation -> fluid loss, respiratory alkalosis, NaHCO3 excretion (more fluid loss)
      * Metabolic: heat production by uncoupled mitochondria=hyperthermia, sweating=fluid loss. Glycolysis stimulated-> glycogen depletion and hypoglycemia. Higher CO2, lactate, pyruvate, acetoacetate = metabolic acidosis
    - Severe tox (110-160 mg/dL)
      * CNS: less respiration = respiratory acidosis and then HCO3- depletion. Blood pH decrease and salicylate to brain -> coma.
    - Lethal tox (>160mg/dL)
      * Metabolic: hyperthermia/dehydration and death
      * Kidney: renal failure and death
      * CNS: respiratory failure and death
    - Treat tox: reduce temp, analyze blood, treat dehydration/electrolyte imbalance, charcoal to minimize absorption. Maximize elimination by alkalinizing urine w/ NaHCO3 infusion
* **ASPIRIN, ACETYL-SALICYLATE, ASA** 
  + Acetylates active site of COX-> irreversible inhibition
  + potent anti-platelet for preventing MI and CVA
* **SALICYLATE** 
  + Acid is keratolytic and used topically to tx warts.
* **IBUPROFEN, KETOPROFEN AND NAPROXEN** 
  + Propionic acid derivatives, less intense side effects (OK in kids)
  + Used for pain, fever, menstrual pain and inflammation OTC
  + Ibuprofen half life 1-2h, ketoprofen 1-3h, naproxen 14h (less dosing)
* **INDOMETHACIN** 
  + Acetic acid derivative
  + Potent inhibitor of COX1, higher incidence of GI effects than aspirin
  + Special short term use only: close ductus arteriosus in premature infants, tocolysis, acute gouty arthritis
* **SULINDAC** 
  + Acetic acid derivative
  + Prodrug converted to active sulfide in liver; undergoes enterohepatic cycling so actions last 16h
  + Less GI tox than aspirin
* **DICLOFENAC** 
  + Used for osteoarthritis and rheumatoid arthritis
  + GI toxicity risk similar to aspirin
  + Multiple formulations include rapid release, extended release etc
* **NABUMETONE** 
  + Low COX1, more selective COX2 so less incidence of GI prob, less ulcers
  + Primarily for antiinflamm for osteoarthritis and rheumatoid arthritis
  + Prodrug converted to active in liver
* **CELECOXIB** 
  + COX2 specific inhibitor, less GI damage w/o loss of analgesic or antiinflamm properties
  + No effect on platelets
  + Treat: RA, osteoarthritis, juvenile arthritis, ankylosing spondylitis, acute pain and menstrual pain, (previously used to reduce number of polyps in familial adenomatous polyposis until 2011)
  + Possible drug interactions since inhibits CYP2D6 and itself is metabolized by CYP2C9
* **ACETAMINOPHEN** 
  + NOT an NSAID, no clinically useful antiinflamm properties (very weak effect) (mech seems to be COX2 inhibition but there is much debate on actual mechanism according to Wikipedia, not sure what we were taught in class?)
  + Only shares antipyretic and analgesic properties of NSAIDs (also no tolerance or dependence develops)
  + Different than aspirin: no CNS effects, no Reye’s syndrome, no cardiovascular or respiratory effect, no GI problems, no effect on platelets, no effect on uric acid secretion
  + Toxicity: very little at low doses, hepatotoxicity at 10-15g, death at 20-25g
* **N-ACETYLCYSTEINE** 
  + At toxic doses of acetaminophen or when taken with alcohol, there is a depletion of glutathione and the toxic intermediate of acetaminophen interacts with cell proteins causing cell death.
  + This drug will provide an alternate substrate for the toxic intermediate and it restores glutathione
  + Will NOT restore damage already done
  + Side effects: N/V/D in oral therapy, if given IV could have anaphylactoid reaction or N/V

**DRUG NAMES TO KNOW AND REMEMBER IN SEX STEROID PHARMACOLOGY**

* **GONADOTROPIN RELEASING HORMONES**
  + **GnRH—**secreted by the hypothalamus in pulses—every 1.5 hours🡪 FSH and LH secretion. One cycle induced ovulation in amenorrheic woman or to treat delayed puberty. Continuous release= suppression. Short half-life to work in pulsatile fashion. Synthetic = **GONADORELIN** (Longer half-lives, Higher receptor-binding affinities –more potent drugs).
    - **LEUPROLIDE =** synthetic GnRH but more potent than gonadorelin. Gly at position 6 allow for tighter binding of compounds🡪 leading to hyper potency. Substitution at Gly at position 10 gives longer half lives so long half life. Continuous use to suppresses LH and FSH. Used in in vitro fert to suppress the LH and FSH and then give urofollitropin and hCG for follicle dev and ovulation. Also used to suppress precocious periods, endometriosis (to suppress the overstimulation of estrogen), and prostate cancer and BPH (to suppress growth of cancer by testosterone).
* **GONADOTROPINS** 
  + **UROFOLLITROPIN** 
    - Menotropin. Only FSH activity. Cheaper than recombinant FSH. Leuprolide is used in vitro to suppress the LH and FSH and then give urofollitropin and hCG for follicle dev and ovulation.
  + **hCG**
    - Isolated from urine of pregnant women. Secreted by placenta🡪 goes into the maternal blood stream🡪 gets secreted by the kidneys in the moms urine. Has LH activity (causes ovulation and progesterone secretion). Cheaper than recombinant hCG. Leuprolide is used in vitro to suppress the LH and FSH and then give urofollitropin and hCG for follicle dev and ovulation.
* **ESTROGENS** 
  + **ALL USED FOR**:
    - Intractable Dysmenorrhea (not treated by NSAIDS, use progestin w/ it) , Hirsutism, Contraception, Menopause (ERT w/ progestins), Postmenopausal osteoporosis (estrogen + progestin; Second line drugs after bisphosphonates) , HRT (only for 5 years)
  + **ESTRADIOL**
    - Secreted by the ovaries and adrenal glands. Is the dominant estrogen secreted. Dominant estrogen that is controlling the female reproductive cycle. Pharmacologically 17 β estradiol is hardly ever used. Quickly inactivated by liver by conjugation (sulfation and glucoronation). Rapid elimination by kidneys. No oral admin.
  + **CONJUGATED-ESTROGEN**
    - Circa 60% **SULFATED ESTRONE**—even thought they’ve been sulfated they still bind to the estrogen receptor and still work but you have to use them at higher doses. Nice thing about these is they have already passed metabolism by the liver (where they were sulfated) making them orally effective at high concentrations. Common drug: **PREMARIN**® (Wyeth) **PREMARIN + PROGESTIN = PREMPRO**® (Wyeth)
  + **ETHINYL ESTRADIOL** 
    - Synthetic, steroidal estrogen. Dominant synthetic estrogen in oral contraceptive pills Potent agonists at the estrogen receptor. Less-rapidly metabolized by liver 🡪 Longer duration of action. Orally effective
  + **DIETHYLSTILBESTROL (DES)**
    - Moderately potent agonist, Slowly inactivated by liver, orally effective, common in past usage. The structure of this compound doesn't look like it’d be an agonist at the E receptor but the two ethers actually form a benzene ring in space and the structure begins to look like a steroid. Causes vaginal adenosis and vaginal clear cell adenocarcinoma in the children of the mothers who took this.
* **BISPHOSPHONATES** 
  + **ALENDRONATE**
    - These drugs slow dissolution of hydroxyapatite crystals. They go into bone and replace the pyrophosphate with this🡪it becomes part of the bone crystal structure. The reason they prevent bone loss is b/c these compounds stabilize the bone mineral, they are less likely to be cleaved, etc leading to much slower turn over rate of bone mineral. Doesn't accumulate and no side effects. Used in Paget’s bone disease as well as post menopausal osteoporosis. Used to also treating hypercalcemia that arises from certain kind of Malignancies/cancer. Also shown useful in preventing male vertebral fractures
* **SERMS** 
  + **TAMOXIFEN**
    - Used to treat **Estrogen receptor positive**—these are not the best kind b/c they grow slower) and they are stimulated to grow by estrogens so you can slow down the growth by txing with a E receptor antagonist. Inhibits estrogen stimulation of cancer growth Can be used on pre- and post-menopausal women with ER- positive tumors. Shown to be just as effective a chemotherapy. Many fewer serious or unpleasant side effects. DOC. Side effects: Hypercalcemia, Bone pain, and Increased risk of endometrial cancer—this is an agonist effect which is weird b/c we call this drug an antagonist. It is acting like an estrogen in the uterus
* **AROMATASE INHIBITORS** 
  + **ANASTROZOLE**
    - Binds reversibly and is a **competitive non-steroidal** inhibitors of aromatase responsible for conversion of androgens to estrogens. Aromatase is responsible for conversion of androgens to estrogens so if you block this enzyme this conversion does not take place so you don't make estrogens.
* **PROGESTINS** 
  + **PROGESTERONE**
  + **MEDROXYPROGESTERONE ACETATE**
    - Derivative of progesterone. These are true progestational agents🡪 Can stimulate endometrial secretions and support pregnancy in test animals. Variable androgenic and estrogenic side effects (draw back of these drugs)
  + **NORETHINDRONE & L- NORGESTREL (this one is becoming more popular)**
    - Derivates of nortestosterone. Can stimulate cellular changes in endometrium but CANNOT support pregnancy in test animals b/c these agents do not cause differentiation of the endometrium into the secretory state which is needed for implantation. More effective inhibitors of gonadotropin secretion (so inhibits ovulatory cycle by inhibiting HP axis). Majority of oral contraceptives now use nortestosterone derivative. Late generation analogs have reduced androgenic and estrogenic side effects
* **ANTIPROGESTINS**
  + **RU486**
    - Anti-progestin. Abortifacient (used to induce abortions). Now used w/ prostaglandin E1 95% effective in inducing abortions. Binds both progesterone and glucocorticoid receptors - preventing gene transcription. Also very good antagonist at glucocorticoid receptor but its typical used to block progesterone receptor Other potential therapeutic uses: Inhibition of progesterone- and glucocorticoid-dependent tumor (like fibroid tumor)s, Cushing’s disease, Post-coital birth control.
  + **FINASTERIDE**
    - Androgens drug. Blocks the enzyme that converts testosterone to DHT in target cells. **PROSCAR**® - Benign prostatic hyperplasia - 5 mg/day = $0.47/mg –CHEAPER. **PROPECIA**® - Male-pattern baldness - 1 mg/day = $1.67/mg
* **CONTRACEPTIVES**
  + **Transdermal Contraceptive**
    - Ortho Evra = the patch. Norelgestromin (active metabolite of norgestimate) and ethinyl estradiol. Patch applied weekly. Advantages: Bypasses hepatic metabolism, Lower peak plasma concentrations of drug than COCs, Presumed lower rates of side effects, Better compliance, Comparable failure rates to COCs in typical usage. Disadvantages: Skin allergies --but can rotate patch placement to get around this, Higher steady state concentrations of drug than COCs
  + **Combined Oral contraceptives (COC)**
    - Can be Monophasic: Constant dose of estrogen + progestin over 21 days; Diphasic and triphasic—these were developed to deal with the problem of irregular spotting associated with the monophasic approach. **Diphasic**: progestin dose increased once at approx. day 10, higher dose maintained to day 21.Most common is **Triphasic** - Progestin increased in 2nd and 3rd week of 21 day dosing regimen
    - Progestin-Only (“Mini-Pill”) Low dose of progestin;Taken every day—fairly effective
    - Most commonly used drugs:✶Estrogen**: ETHINYL ESTRADIOL** (Estinyl®)  Progestin: **NORETHINDRONE** (Norlutin®), **L-NORGESTREL** (Ovrette®)
  + **Post coital**
    - **CONJUGATED ESTROGENS**, **ETHINYL**  **ESTRADIOL.** Effective when begun by 72 hours post-coitum (after sex). New studies suggest that 3rd generation progestins, like plan B (L-NORGESTREL) are more effective**.** Effectiveness: 89% (72 hours), 95% (24 hours)  Mechanism – Delays ovulation and sperm migration, found not to disrupt implantation. In women who have ovulated Plan B has no protective effect b/c it doesn't block implantation or fertilization of egg. Strong side effects –these are minimized w/ Plan B though; Nausea, Vomiting, Severe cramps.
  + **Intradermal**
    - **NORPLANT II**® (Jadelle®) = Two flexible capsules containing **NORGESTREL (3rd generation progestin).** Inserted under skin on upper arm or thigh. Require minor surgery with local anesthetic. Effective for up to 5 years. Serum steroid levels are 1/5 to 1/3 of oral contraceptives w/ Fewer side effects. Effectiveness: After One Year: 0.2 failures per 100 women years. After Five Years: 0.8 failures per 100 women years—same as COC

**DRUG NAMES TO REMEMBER /RECOGNIZE—IMMUNOLOGICS**

* **METHOTREXATE**
  + DOC for RA. Orally 1xper week. Blocks DHFR to inhibit purine synthesis. Contraindicated in pregnancy (Cat X)! Toxicity offset w/Leucovorin or folate by increasing THF.
* **LEUCOVORIN** 
  + Given 24 hours after MTX to lower the side effects. It works like folate to increase the THF so that the slower dividing cells can continue division. Also potentiates fluorouracil chemotherapy.
* **AZATHIOPRINE**
  + Blocks DNA and RNA synthesis. Used for RA, renal transplants. Oxidized by xanthine oxidase therefore drug interaction with Allopurinol which blocks that enzyme. Category D for fetus so causes harm and only can be used if benefits >risks.
* **ETANERCEPT** 
  + soluble TNFa “receptor” antibody chimera. SC injection 1-2x/week. Used w/or w/o MTX. SE= risk of infections & latent TB, live vaccines contraindicated, neuro issues w/demyelinating diseases (MS), increased malignancy and lymphoma in kids, autoimmunity.
* **INFLIXIMAB** 
  + Chimeric TNFa Ab.IV infusion once/8 weeks. Used w/MTX for RA, Crohn’s, & ulcerative colitis. SE= risk of infections & latent TB, live vaccines contraindicated, neuro issues w/demyelinating diseases (MS), increased malignancy and lymphoma in kids, autoimmunity.
* **CYCLOSPORINE** 
  + GI tract has trouble absorbing them (↑ partition coeff)—need to dissolve them in an ethanol mix to try and get some uniform absorption. ***USES*** Prevent rejection in renal, liver and heart transplants *VERY IMPORTANT;* Autoimmune diseases RA, IBD, myasthenia gravis; Can be used in conjunction with glucocorticoids (prednisone) and azathioprine (or could replace this w/ mycophenolate which has fewer side effects) ***MECHANISM*** T-cells get activated by the APC (w/ second signal from B7 on APC and CD28 on T-cell 🡪 ↑ Ca). Signal transduction involves an increase in cytosol Ca2+, which activates **calcineurin** (Cal), a phosphatase that dephosphorylates NF-AT (nuclear factor of activated T-cells)—the phosphate normally hides the target sequence that can allow it to go into the nucleus. NF-AT can now enters the nucleus and turns on synthesis of cytokines such as interleukin-2 and its receptor, which induces T-cell proliferation. **Cyclosporine binds to a cyclophilin (CP) and inhibits calcineurin, thus inhibiting T-cell activation/proliferation (**so blocks formation and activity of IL-2) ***PHARMACOKINETICS:*** 1st pass metabolism significant - metabolized by **CYP3A4** and  substrate for **P-gp** (kicks hydrophobic things out of cells) ***TOXICITY* Nephrotoxicity most common and important** (20-38% in allografts). Difficult to distinguish from kidney rejection in kidney transplant patients. Hypertension—50% of patients w/ kidney transplant & 100% of patients w/ heart transplan; Hirsutism; Little effect on bone marrow (Many of the cytotoxic drugs (like azathioprine) do have toxic effects on bone marrow so you don't really want 2 drugs with same side effects b/c it ↑ the likelihood of them occurring) ***DRUG INTERACTIONS - IMPORTANT –*b/c narrow therapeutic window** Drugs that inhibit CYP3A4 or P-glycoprotein may **potentiate toxicity** 
    - ketoconazole, itraconazole, (antifungals)
    - erythromycin, clarithromycin, grapefruit juice (esp in GI tract), etc.
    - Ritonavir is most efficacious inhibitor of CYP3A4
    - Cyclosporin itself inhibits CYP3A4
  + Drugs that induce the CYP3A4 or P-gp may lead to **organ rejection** b/c will be metabolized faster and level of drug in the body will ↓
    - Phenobarbital - CNS depressant
    - Carbamazepine - anticonvulsant
    - Phenytoin-anticonvulsant
    - Rifampin - antimicrobial used for tx Tb
    - **St. John’s Wort** - dietary supplement - “antidepressant”
  + Other nephrotoxic drugs
    - e.g. amphotericin B, aminoglycosides, NSAIDs etc
  + Cyclosporine can inhibit metabolism of drugs by blocking CYP 3A4
    - E.g. lovastatin – increases risk of rhabdomyolysis
* **TACROLIMUS (FK506, *Prograf*®, 1994)**
  + inhibits calcineurin—it is very similar to cyclosporine. Properties **very similar to cyclosporine**, ***BUT*** has different receptor - “FK binding protein” (FKBP25) 🡪 inhibition of IL-2 production and IL-2 receptor production. Approved for heart, liver and kidney transplants to ↓ rejection. Used topically for treating eczema
* **SIROLIMUS (*Rapamune*®, 1999)**
  + U**sed synergistically with cyclosporine and prednisone. *MECHANISM*** Binds to a “FK binding protein”, FKBP12, but unlike cyclosporine and tacrolimus it does ***NOT*** block calcineurin or IL-2 production. It acts at a later step . Block a kinase “mTOR” – a kinase involved in cell cycle . mTOR= Mammalian Target Of Rapamycin—this is a receptor. Blocking this leads to blockage of T-cell proliferation induced by cytokines , Blocks B-cell proliferation and differentiation into Ig producing cells , Blocks proliferation of endothelial and SM cells –so also used for coating stents ***USE*** Prophylaxis of renal transplant rejection; Is used in combination with cyclosporine and corticosteroids –they act at different steps in the pathway; Not for liver transplant - hepatic artery thrombosis risk. ***SIDE EFFECTS*** Little nephrotoxicity alone, **But**, sirolimus aggravates CSA (cyclosporine)-induced renal dysfunction (makes CSA nephrotoxicity worse!); Triglycerides and cholesterol increase (51%, 44%) and further increased by concomitant use of CSA (cyclosporin A= cyclosporine); All patients should be monitored for hyperlipidemia; Increased BP & Thrombocytopenia (37%) –blocks proliferation of a lot of cells. ***DRUG INTERACTIONS -*** Bioavailability is only 14% and metabolized via CYP 3A4, hence susceptible to drug interactions, e.g. cyclosporine (CSA inhibits its metabolism so levels of it will ↑ in the blood). In addition to CSA, many drug interactions possible. Sirolimus normally administered 4 hr after CSA—Don't administer simultaneously ***ADMINISTRATION*** Not soluble in water must be dissolved in an oil base Administered mixed with water or orange juice, **NOT grapefruit**
* **ALLOPURINOL** (see drugs for Gout)
* **MYCOPHENOLATE MOFETIL** 
  + Used for transplants and off-label for RA. Selectively blocks DNA/RNA synthesis in T cells & B cells bc these need de novo synthesis of GTP (blocks guanine synthase). Blocks the proliferation, Ab formation, and lymphocyte activation/migration. SE= GI toxicity, Bone marrow Tox, Minimal nephrotoxicity, Category D for fetus.

**DRUG NAMES TO KNOW/RECOGNIZE FOR GOUT**

* **COLCHICINE**
  + Oral drug. ***MECHANISM—***Binds to tubulin (which makes the spindles during cell division) causing dissociation of microtubules (which help move chromosomes during cell division!). Blocks cell division, motility of cells (recruitment), phagocytosis in neutrophils & macrophages. May block macrophage uptake of the crystals 🡪 ↓ inflammatory response. ***TOXICITY – IMPORTANT—***Blocks cell division in GI tract, bone marrow🡪 Produces nausea, vomiting, diarrhea, abdominal pain. Overdose can be lethal, especially when > 4 mg/day given IV. ***USES—*Treatment of ACUTE attack of gout**– “**High dose”🡪**Pain, swelling, redness usually gone in 48-72 hrs. **Maximum total dose**: 1.8 mg over 1 hr. Higher /additional doses provide no additional relief. **NSAIDs** usually preferred as **fewer side effects. Also used for PROPHYLAXIS of acute gouty arthritis** “**Low dose”🡪** Useful in combination with hypouricemic drugs. Discontinue if symptom free for 1 year. **Maximum dose** 1.2 mg per day. ***DRUG INTERACTIONS*** with CYP3A4 and P-gp inhibitors
* **INDOMETHACIN** 
  + A potent NSAID for short term therapy of gout. Drug of choice, if NSAIDs not contraindicated. Ibuprofen, diclofenac, etc. also effective. As effective as colchicine for an acute attack of gout. If response inadequate, use a glucocorticoid
* **PROBENACID**
  + Renal handling🡪 90% of this drug is bound to albumin, so most is actively secreted into tubule. We saw this before used to ↓ the secretion of penicillin in order to ↑ it’s half life. Undergoes almost complete non-ionic reabsorption. Plasma t½ = 5-8 hrs because as it gets concentrated down the tubule it has a reasonable half life and its gets reabsorbed. ***ACTIONS* Low doses** block anion secretion in kidney, etc. So at low doses you actually block the secretion of uric acid from the blood into the kidney and we don't want this! Developed to inhibit elimination of penicillin **Higher doses** specifically **block urate reabsorption by acting from the inside of the tubule.** 90% of uric acid is reabsorbed in the PCT of the kidney. **Net effect: increased excretion of urate. *CONSEQUENCES OF THERAPY* ↑ excretion of urate ↑ the risk of uric acid kidney stones** To prevent this: Consume 1500 ml water per day to dilute the urine, Administer 3-7.5 g Na HCO3 per day to alkalinize urine until plasma urate is normal ***and*** tophi have disappeared and DO NOT USE if there is *overproduction* of uric acid b/c **Acute gouty arthritis attacks can be precipitated—DO NOT** initiate treatment until acute attack subsided. Combine with ***low dose*** colchicine, e.g. *Col-probenecid*® To promote uric acid excretion
* **SULFINPYRAZONE** 
  + Strong organic acid, pK 2.8. Uricosuric action similar to probenecid. Only other uricosuric drug approved in USA, but marketing discontinued
* **ALLOPURINOL**
  + ***MECHANISM AND PHARMACOKINETICS:*** Allopurinol looks like a purine & is a competitive inhibitor/ substrate of Xanthine oxidase (XO). Allopurinol is oxidized to **oxypurinol** by XO = Result: Allopurinol short t½ = 1-2 hr. **Oxypurinol is a potent non-competitive inhibitor of XO.** Like uric acid, oxypurinol is filtered and reabsorbed 🡪 Result: long t½ = 18-30 hr, long duration of action. ***CONSEQUENCES of THERAPY* Plasma urate** ↓; hypoxanthine↑; xanthine↑ (b/c your blocking their metabolism by XO). Urate in tophi begins to dissolve. More hypoxanthine and xanthine recycled to purines. **Urine urate** ↓; hypoxanthine↑; xanthine↑. Prevents formation of uric acid kidney stones, prevents nephropathy. Although hypoxanthine and xanthine solubility is low, concentration in plasma and urine rarely exceed solubility. These two things are more soluble than uric acid and usually you don't have problems with these but you will still want to maintain ↑ levels of fluids to dilute the urine. ***However;*** to ensure xanthine stones (calculi) **do not** form, urinary output should be maintained at 2L per day and at a neutral or preferably slightly alkaline pH. Incidence of acute gouty arthritis attacks **may actually ↑**  during first months of therapy. **DO NOT** begin therapy during an **acute attack** b/c it will make things worse and. **Use colchicine** (and/or NSAID) until serum uric acid is normal and no attacks for several (3) months, or tophi gone. Attacks decline after tissue stores are reduced—don't need colchicine after this ***ADVERSE REACTIONS* Most serious,** rare but can be **fatal:** Skin rash/fever → i.e. necrolysis, vasculitis, hepatitis, renal failure. ***DRUG INTERACTIONS*** Azathioprine and mercaptopurine (MP). MP is metabolized to thiouric acid by xanthine oxidase so if you use allopurinol the levels of MP in the blood go way up. Administration of allopurinol requires dose↓ to 25-33%. Probenecid and other uricosurics. Inhibit reabsorption of oxypurinol and decrease its half-life ***INDICATIONS*** Patients with **signs and symptoms** of gout, ***not recommended*** for **asymptomatic** hyperuricemia. Patients with leukemia, lymphoma and malignancies receiving chemotherapy 🡪 ↑ purine metabolism that elevates urate
* **FEBUXOSTAT**
  + Xanthine oxidase inhibitor
  + ***DRUG INTERACTIONS***: drugs metabolized by XO (**Azathioprine**, **Mercaptopurine**, Theophylline)
* **RASBURICASE**
  + Recombinant form of URICASE from yeast. Used in Pediatric patients with leukemia, lymphoma, and solid tumors undergoing chemotherapy (expected to elevate plasma uric acid b/c ↑ purine metabolism due to ↑ cell death). Short-term therapy that is done while chemo is going on. Adverse effects: Anaphylaxis
* **PEGLOTICASE**
  + Mammalian URICASE conjugated to PEG (polyethylene glycol). Used in Treatment of gout in adults refractory to XO inhibitors. Have to take IV every 2 weeks. Adverse effects: Severe allergic reaction and sometimes anaphylaxis. Need preinfusion of antihistamines and glucocorticoids to ↓ allergic responses.

**DRUG NAMES TO KNOW/RECOGNIZE FOR SKIN DISEASES**

* **TRETINOIN (Retin-A)**
  + Topical for treatment of acne. It is a comedolytic and inhibits keratinization - promotes expulsion of open comedones (promotes expulsion of sebum from the follicle )🡪 Decreases cohesiveness of epithelial cells in follicle & Decreases thickness of *stratum corneum.* Other uses include--diminishes fine lines and wrinkles (*Renova*®), Promotes dermal collagen synthesis, Promotes new blood vessel formation, Promotes thickening of epidermis. Adverse effects: only 10% is absorbed into circulation so minimal/no systemic effects; ↑ susceptibility to sunburn so use sunscreen (15SPF) and protective clothing. Not usually prescribed to pregnant patients b/c of TERATOGENESIS (see isotretinoin contraindication in preg)
* **ISOTRETINOIN**
  + Systemic retinoic acid. Oral therapy reserved for treatment of severe nodular acne in patients who are unresponsive to conventional therapy, including systemic antibiotics. Very effective tx of acne. Mechanism: ↓ sebum production, ↓ sebaceous gland size, ↓ keratinization, ↓ inflammation.
  + ***ADVERSE EFFECTS***: Similar to those of hypervitaminosis A
    - ON EPITHELIUM/SKIN: Dryness of skin and mucous membranes - results in Dry itchy eyes, nose, mouth, Nose bleeds, inflammation of lips (cheilitis), Less commonly cause Hair loss, peeling of skin from palms and soles, Sensitivity to UV light, use protection against sun, Inflammatory bowel disease
    - HYPERLIPIDEMIA: Elevation of tri-glyceride levels, Sometimes increase in cholesterol (LDL) and decrease in HDLs - needs to be monitored
    - EFFECTS ON BONE FORMATION: Long-term therapy- calcification of ligaments and tendons, Decreased bone mineral density, Pain in joints muscles
    - SUDDEN REDUCTION IN NIGHT VISION: Seems paradoxical
    - PSEUDOTUMOR CEREBRI– RARE: Benign cerebral hypertension, can be mistaken for a tumor 🡪 Leads to edema of optic disk (papilledema), which can lead to permanent blindness—More likely if tetracycline co-administered
    - DEPRESSION - RARE, BUT... Depression and suicidal ideation may be associated with retinoids.
  + ***CONTRAINDICATION***: PREGNANCY--TERATOGENESIS
    - Isotretinoin is a pregnancy category X drug and should not be taken during pregnancy. There is a very high risk of birth defects, e.g. Skull abnormalities, External ear malformation, Facial malformation, Cleft palate, CNS abnormalities, CV abnormalities. *IMPORTANT: To prevent birth defects isotretinoin must be prescribed under the iPLEDGE program—LOTS OF THINGS have to be done to make sure the woman is aware of the side effects and is not at risk of becoming pregnant*
* **ACITRETIN AND ETRETINATE - SYNTHETIC ANALOGS**
  + They are approved for systemic treatment of psoriasis. Their side effects and contraindications are similar to isotretinoin. **ACITRETIN** is the active metabolite of **ETRETINATE** Etretinate (removed from market) accumulates in adipose tissue and has a very long half-life (120 days) compared with acitretin (49 hours). However, if ethanol is consumed by patients taking acitretin, etretinate is synthesized, consequently, alcohol should be avoided. Also, patients should not become pregnant for at least 3 years after the last dose or donate blood. Mechanism in Psoriasis**:** Inhibits proliferation of epithelial cells, Inhibits keratinization of epithelial cells, Inhibits differentiation of epithelial cells
* **TAZAROTENE**
  + Tazarotene is a synthetic retinoid. It is a prodrug, which is hydrolyzed to produce a carboxylic acid – tazarotenic acid – the active drug. It is used topically for the treatment of both acne and psoriasis. First topical retinoid approved for psoriasis and wrinkles.
* **BEXAROTENE**
  + Bexarotene is a drug that is a selective agonist for retinoid X receptors (α, β, γ), and does not activate RAR receptors. It Inhibits growth of tumor cell lines of hematopoietic and squamous cell origin. Used for treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients resistant to one prior systemic therapy. Contraindicated in pregnancy. Side effects: ↑ of TGs, LDL cholesterol & hypothyroidism